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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/434,870	11/04/1999	WILLIAM D. HUSE	P-IX-3458	4474

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/13/2002 22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/434,870	HUSE ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 20 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Request for Continued Examination

1. The request filed on 3/29/02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/434870 is acceptable and a RCE has been established. Claims 42-71 are pending and are currently under prosecution. An action on the RCE follows.

2. Claims 42 and 47 have been amended.

Claims 52-71 have been added.

3. Claims 42-71 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action

5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 42-51 under 35 USC 112 first paragraph is withdrawn in view of the declaration by Dr. Watkins.

7. The rejection of claims 42-51 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of arguments.

8. The rejection of claims 42-51 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims and arguments.

9. The rejection of claims 42-51 under 35 U.S.C. 103(a) as being unpatentable over Deng et al (Canadian Patent 2,125,240 A1, published 12/7/95, IDS #8) is withdrawn in view of the new grounds of rejection.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

10. Claims 42-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 42, 44-47, 49-52, 54-57, 59-62, 64-67, 69-71 are indefinite for reciting "providing a representation" in claims 42, 47, 52, 57, 62, 67 because the exact meaning of the phrase is not clear. Does the phrase mean a picture, a sequence on paper, a thought pattern?

b. Claims 42, 47, 52, 57, 62, 67 recites the limitation "said acceptor framework region reference sequence" and "said framework positions" and "said acceptor framework positions" in the claims. There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 103

11. Claims 42-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deng et al (Canadian Patent 2,125,240 A1, published 12/7/95, IDS #8) and further in view of Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and Hagiwara et al (U.S. Patent 5,589,573, issued 12/1996).

The claims recite a method of constructing a population of heavy or light chain variable region encoding nucleic acids comprising providing a donor sequence and an acceptor sequence and chemically synthesizing a population of oligos encoding for at least one modified CDR wherein at least one amino acid is different from the reference sequence and a second population of oligos encoding modified framework regions wherein one or more amino acids are changed compared to the reference sequence and mixing and constructing the nucleic acids. Further co expressing the population with a light or heavy chain and wherein the acceptor is human and the representation is in electronic form and further the method comprises extending the oligos with DNA polymerase and the mutagenesis is by codon-based mutagenesis.

Deng et al teach a method of producing a population of heavy or light chains wherein the CDRs are randomized and the framework regions are randomized (see page 12, lines 28-32, Figure 2, page 22-23) and the method is a library approach where the residues that differ between the mouse and human framework are randomized (see page 13, lines 4-16). The method comprises chemical synthesis of oligos and framework regions are randomized wherein the residues randomized are those that

differ between the murine and the human (see page 22-23) and mixing oligos to construct the nucleic acid library and the method comprises PCR which uses a DNA polymerase (see page 8, lines 21-24). Deng does not specifically teach that the reference sequences are in electronic form or codon-based mutagenesis. Theses deficiencies are made up for in the teachings of Yelton et la and Hagiwara et al.

Yelton et al teach affinity maturation of an antibody by codon based mutagenesis and construction of random libraries in the heavy chain and they intend to examine the light chain (see entire document and page 2002, left column).

Hagiwara et al teach amino acid sequences from a database of Kabat et al and the sequences are retrievable by computer (see column 12, lines 25-40).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have the first and second reference sequences to be in electronic form and to use codon based mutagenesis.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have the first and second reference sequences to be in electronic form and use codon based mutagenesis because Yelton et al teach affinity maturation of antibodies with codon based mutagenesis (see entire document, especially page 1995, left column) and Yelton teaches "codon-based mutagenesis efficiently introduces large numbers and potentially all combinations, of amino acid substitutions into a specifically targeted region, such as a CDR" and "mutagenic methods such as error-prone PCR or chemical mutagenesis are less efficient for introducing all possible substitutions at a given position" (see page 1995, left column)

and Deng et al teach the level of spiking will vary depending on the individual situation and the desired frequency of amino acid substitutions (see page 9, lines 9-18 of Deng et al). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have the first and second reference sequences to be in electronic form because Hagiwara et al teach amino acid sequences from a data base of Kabat et al and the sequences are retrievable by computer (see column 12, lines 25-40). In addition, because the database is accessible by computer it would be obvious to download the sequences onto an electronic form for storage and manipulation.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 3/29/02 has been carefully considured but is deemed not to be persuasive. The response argues first that Deng et al does not introduce a modification at one or more framework region positions wherein the positions changed are selected from those which differ between a reference acceptor sequence and the reference donor sequence. In response to this argument, Deng et al teaches mutagenesis in both the CDRs and the frameworks with randomization of the DNA sequence at specified locations in the sequence (see pages 1, 4, 7-8). The response further argues that codon based mutagenesis is used in claims 62 and 67. In response to this argument, while this is true, other claims do not require this limitation and with regard to this limitation the art of Yelton et al clearly teaches codon based mutagenesis

and the advantages of using this strategy for affinity maturation (see page 1995). In addition, Deng et al teach that the level of spiking will vary depending on the individual situation and the desired frequency of amino acid substitutions (see page 9, lines 9-18). Thus, it would have been obvious if it was desired to totally randomize the oligos to use codon-based mutagenesis because of the advantages taught by Yelton et al. The response further argues that Deng et al does not teach that framework residues that were altered are those that differ between the murine and the human and the response argues that "actual" differences between the two reference sequences are used in the claimed method (see page 14 of response). In response to this argument, the claims recite "framework positions that are changed are selected from among said acceptor framework positions of said second reference sequence that differ at the corresponding position compared to the donor framework positions" (see claim 42). Deng et al clearly teaches randomization in the frameworks that differ between the mouse and human (see page 22-23 of Deng et al). The response states that the method of Deng et al suggests consensus sequences rather than a direct comparison (see page 14). In response to this argument, this is speculation and even so if the consensus human sequence would differ from the mouse sequence, Deng et al clearly teaches changing the sequence and randomization based on comparing two sequences, NEW and the murine frameworks. Lastly the response argues claims 52 and 57 require the use of a polymerase to assemble the overlapping oligos. In response to this argument, Deng et al teach PCR of the DNA and Deng et al teach overlapping oligonucleotides can be used in the method which eliminate the template DNA (see page 8, lines 6-10) and it

would have been obvious to use PCR to amplify the DNA after the primers are annealed to the DNA. Finally the response argues that an affidavit is required as evidence of facts for using sequences in electronic form. In response to this argument, the reference of Hagiwara et al teaches databases of antibody sequences and it would be obvious to place the sequences in an electronic form for comparison and storage and such databases are known as taught by Hagiwara et al.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

SHEELA HUFF
PRIMARY EXAMINER